Exhibit B

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

MITSUBISHI TANABE PHARMA CORPORATION, JANSSEN PHARMACEUTICALS, INC., JANSSEN PHARMACEUTICA NV, JANSSEN RESEARCH AND DEVELOPMENT, LLC, and CILAG GMBH INTERNATIONAL, Plaintiffs, v. ZYDUS PHARMACEUTICALS (USA) INC., Defendant.	**Civil Action No. 17-5005 (consolidated)** **Contains Highly Confidential Information**

OPENING EXPERT REPORT OF ERIC J. MUNSON, PH.D.

I, Eric J. Munson, submit the following report on behalf of Mitsubishi Tanabe Pharma Corp., Janssen Pharmaceuticals, Inc., Janssen Pharmaceutica NV, Janssen Research and Development, LLC, and Cilag GmbH International (collectively, "Plaintiffs") in this action.

I. EXPERT QUALIFICATIONS

1. I am an expert in the field of pharmaceutical sciences, including the characterization of pharmaceuticals using various analytical techniques, with a specialty in the area of nuclear magnetic resonance ("NMR"), including both solution NMR and solid-state NMR spectroscopy ("SSNMR").

2. I graduated, *summa cum laude*, from Augustana College, Sioux Falls, South Dakota in 1987 with a Bachelor of Art degree in both Chemistry and Physics and a minor in Mathematics. I was also a Fulbright Fellow at the Technical University of Munich, Munich, West Germany from 1987-1988.

3. In 1993, I obtained a Ph.D. in Chemistry from Texas A&M University. My dissertation was in the field of solid-state NMR spectroscopy entitled "In Situ Solid-State Nuclear Magnetic Resonance Studies of Reactions in Zeolite Catalysts."

4. Currently, I am the Dane O. Kildsig Chair and Head of the Department of Industrial and Physical Pharmacy at Purdue University.

5. Prior to my current position at Purdue University, I was employed by the University of Kentucky, where I was the Patrick DeLuca Endowed Professor in Pharmaceutical Technology in the Department of Pharmaceutical Sciences from 2010-2018. Prior to 2010, I was employed at the University of Kansas for nine years, where I held the positions of Associate Professor, Courtesy Professor, and Professor in the Department of Pharmaceutical Chemistry. From 1994-2001, I was employed at the University of Minnesota in the Department of

Chemistry, where I held positions as an Assistant Professor, Associate Member of the Graduate Faculty, McKnight Land-Grant Assistant Professor, and Associate Professor. In addition, from 1993-1994, I was a Postdoctoral Associate at the University of California, Berkeley in the Department of Chemistry.

6. I am a member of various professional societies, including the American Chemical Society, the American Association of Pharmaceutical Scientists, and the American Association for the Advancement of Science.

7. I have also consulted with drug companies, both brand name and generic, on the characterization of pharmaceutical compounds and compositions. In addition, I have assisted both brand name and generic companies with litigation relating to pharmaceutical products.

8. In addition, I am a named co-inventor on three issued U.S. patents that all relate to NMR spectroscopy.

9. For a more complete list of my publications and patents, please see my curriculum vitae attached hereto as Exhibit 1.

10. I received a National Science Foundation Predoctoral Fellowship from 1988-1991. In 1991, I received the American Chemical Society Division of Analytical Chemistry Graduate Fellowship Award and the Society for Applied Spectroscopy Graduate Student Award. In 1993, I received the Texas A&M University Outstanding Graduate Research Award. I received the National Science Foundation CAREER Award in 1996. In 2003, I received the Pfizer Research Scholar Award. In 2009, I was a Fellow at American Association of Pharmaceutical Scientists. In 2014, I received the Research Achievement Award from the Analysis and Pharmaceutical Quality Section of the American Association of Pharmaceutical Scientists (AAPS).

11. From 2012-2015, I was an associate editor for the journal *Molecular Pharmaceutics*.

12. For a more complete list of my honor and awards, please see my curriculum vitae attached hereto as Exhibit 1.

13. I have given over 200 invited lectures on the topics of SSNMR, including, but not limited to, SSNMR of pharmaceuticals, SSNMR studies of polymorphism, new techniques for SSNMR studies, and SSNMR spectroscopy to characterize polymorphs.

14. For a more complete list of my invited lectures, please see my curriculum vitae attached hereto as Exhibit 1.

15. I have also published in the areas of X-Ray Powder Diffraction ("XRPD") analysis, including publications that include both SSNMR and XRPD data as techniques to characterize polymorphic forms of compounds:

- Padden, B. E.; Zell, M. T.; Dong, Z.; Schroeder, S. A.; Grant, D. J. W.; Munson, E. J. "Comparison of Solid-State NMR Spectroscopy and Powder X-Ray Diffraction for Analyzing Mixtures of Polymorphs: 1. Neotame", *Anal. Chem.* 1999, *71*, 3325-3331;
- Liang, Jingmei; Ma, Yue; Chen, Bin; Munson, Eric J.; Davis, H. Ted; Binder, David; Chang, Hung-Ta; Abbas, Syed; Hsu, F.-L. "Solvent modulated polymorphism of sodium stearate crystals studied by X-ray diffraction, solid-state NMR, and cryo-SEM", *J. Phys. Chem. B* 2001, *105*, 9653-9662;
- Delaney, S.P.; Nethercott, M.J.; Mays, C.J.; Winquist, N.T.; Arthur, D.; Calahan, J.L.; Sethi, M.; Pardue, D.S.; Kim, J.; Amidon, G.; Munson, E.J. "Characterization of Synthesized and Commercial Forms of Magnesium Stearate Using Differential Scanning Calorimetry, Thermogravimetric Analysis, Powder X-Ray Diffraction, and Solid-State NMR Spectroscopy", *J. Pharm. Sci.*, 2017, *106*, 338-347.

16. I am being compensated at my usual rate of $350 per hour in connection with this proceeding. My compensation does not depend in any way on the outcome of this litigation.

II. PREVIOUS TESTIMONIAL EXPERIENCE

17. In the last four (or more) years, I have provided expert testimony at trial or by deposition in the following cases:

- *Bristol-Myers Squibb Company and Pfizer Inc. v. Aurobindo Pharma USA Inc.* (Case No. 17-374-LPS-consolidated, D. Del.)
- *Novartis Pharmaceuticals Canada Inc. v. Teva Canada Limited and The Minister of Health* (Court File No. T-1260-16);
- *Merck Sharp & Dohme Corp. v. Fresenius Kabi USA, LLC., et al.* (Case No. 14-4989 (SRC)(CLW)); and
- *Merck Sharp & Dohme Corp. v. Xellia Pharms. Aps., et al.* (Case No. 14-199-RGA (D. Del.)).

III. BASES FOR OPINIONS

18. The opinions presented below are based upon my education, experience, and consideration of the information and materials referred to herein, as well as those listed in Exhibit 2. Exhibit 2 includes a table identifying the exhibits cited in this report.

IV. OVERVIEW OF OPINIONS

19. I understand that the Defendant Zydus Pharmaceuticals (USA) Inc. ("Zydus") seeks permission from the United States Food and Drug Administration ("FDA") to market generic versions of Invokana® through its submission of Abbreviated New Drug Application No. 210541 ("the '541 ANDA"). In addition, I understand that Zydus has submitted Abbreviated New Drug Application No. 210542 ("the '542 ANDA") seeking to market generic versions of Invokamet®.

20. [redacted]

21. I also have been asked to consider whether samples of Zydus' active pharmaceutical ingredient ("API"), tablets described in Zydus' '541 ANDA, and tablets described in Zydus' '542 ANDA contain the crystalline canagliflozin hemihydrate form shown by Figure 1 of the '582 patent. In my opinion, samples of Zydus' API and samples of the tablets described in Zydus' '541 ANDA and '542 ANDA contain crystalline canagliflozin hemihydrate, and specifically, crystalline canagliflozin hemihydrate as shown by the XRPD pattern of Figure 1 of the '582 patent.

22. I have been asked to consider whether the drug products described in Zydus' '541 ANDA and '542 ANDA infringe claims 1 and 3 of the '582 patent. In my opinion, those drug products infringe claims 1 and 3 of the '582 patent.

23. I am also prepared to serve in a teaching capacity to discuss scientific principles relating to my areas of expertise, as well as the level of ordinary skill in the art at the relevant time(s) and background relating to the issues discussed herein, if asked to do so.

V. A PERSON OF ORDINARY SKILL IN THE ART

24. I was asked by counsel to use December 4, 2006, the filing date of the provisional application to which the '582 patent claims priority, as the relevant date for my analysis. While my report is based on that date, my opinions would not change if I used December 3, 2007, the non-provisional filing date of the '582 patent, as the relevant date for my analysis.

25. In my opinion, as of either December 4, 2006 or December 3, 2007, a person of ordinary skill in the art ("POSA") would be (a) a person with an advanced degree in chemistry, analytical chemistry, physical chemistry, organic chemistry, pharmaceutical chemistry, medicinal chemistry, or chemical engineering, and with at least two years of experience developing, characterizing, and/or analyzing pharmaceutical compounds and products; or (b) a

person with a bachelor's degree in one of those disciplines and several years of practical experience in researching, developing, characterizing, and/or analyzing crystals and/or polymorphs in solid-state chemistry. I am a person of at least ordinary skill under this definition. The opinions I express in the report are from the viewpoint of a POSA as I have defined it.

VI. LEGAL STANDARDS REGARDING PATENT INFRINGEMENT

26. In forming my opinions in this case, I used the following legal standards that were provided to me by counsel.

27. I understand that the plaintiff bears the burden of proving patent infringement by a preponderance of the evidence. It is my understanding that the plaintiff must show that the defendant's accused product meets each and every claim limitation properly construed.

28. I understand that it is an act of infringement to submit an ANDA for a drug product claimed in a patent or the use of which is claimed in a patent. It is my further understanding that it is an act of infringement to make, use, sell, offer to sell, or import into the United States a product claimed by a patent. It is my further understanding that in the context of an ANDA, the question for infringement is whether, if the drug product in question were approved based on the ANDA, would the manufacture, use, sale, or offer to sell that drug product infringe the patent. Put differently, the question is whether the products that are made, used, sold, or offered for sale pursuant to that ANDA will likely include products that infringe.

29. I understand that infringement involves a two-step analysis. The first step is determining the proper construction of the asserted claims. I have reviewed the claim constructions that have been adopted in this case, as I discuss below.

30. I understand that the second step in the infringement analysis is to compare the properly construed claims to the accused products. The accused products infringe if they meet every element of a properly construed claim.

31. I understand that the Court has issued a claim construction order in this case. I understand that the Court has ruled that the term "crystalline form of 1-(β-D-glucopyranosyl)-4-methyl -3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate," as it appears in claims 1 and 3 of the '582 patent means "a crystalline form of 1- (β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene comprising approximately half a mole of water to one mole of the compound". (Ex. 4, *Markman* Order at Dkt. No. 237.)

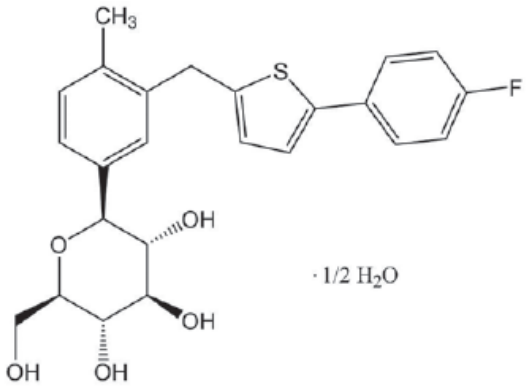
32. I have considered and applied the Court's Claim Construction in my analysis of the '582 patent. To the extent any terms of the claims have not been construed by the parties or the Court, I understand that those claim terms should be interpreted as they would have been understood by a POSA at the time of the respective patent applications.

VII. BACKGROUND

A. The '582 patent

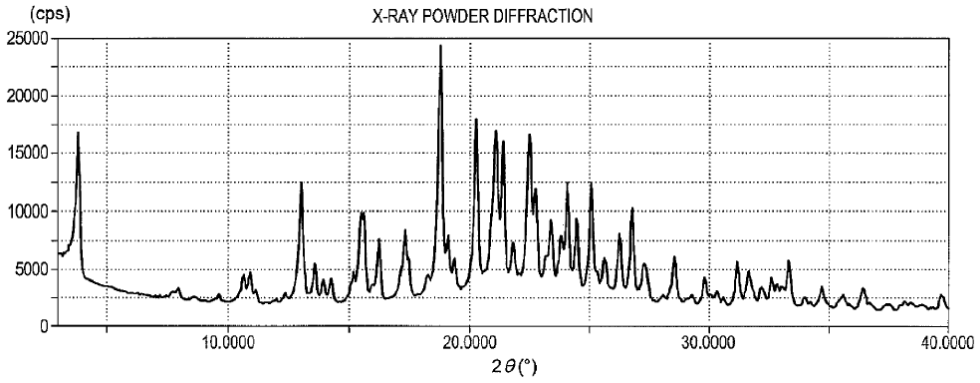
33. The '582 patent is entitled "Crystalline form of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate." 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene is a chemical name for canagliflozin.

34. Canagliflozin hemihydrate has the following chemical structure:



(Ex. 20)

35. Figure 1 of the '582 patent is an XRPD[1] pattern of an embodiment of crystalline canagliflozin hemihydrate:



(Ex. 3 at Fig. 1).

36. Claim 1 of the '582 patent recites: "A crystalline form of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate."

37. Claim 3 of the '582 patent recites: "A crystalline form of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate of claim 1, having substantially the same X-ray diffraction pattern as set out in FIG. 1."

[1] XRPD can also be referred to as PXRD, powder X-ray diffraction, or powder-XRD.

B. Zydus' Proposed ANDA Products

38. I understand that upon receiving approval from the FDA of its '541 and '542 ANDAs, Zydus intends to market its products covered by those ANDAs in the United States. I refer to those products collectively as "Zydus' ANDA Products," and I refer to products covered by the '541 ANDA as "Zydus' '541 ANDA Products," and products covered by the '542 ANDA as "Zydus' '542 ANDA Products."

39. Zydus' '541 ANDA Products include two dosage strengths—a 100 mg tablet and a 300 mg tablet, which are manufactured from a common blend. Zydus' '541 ANDA states that the API in the '541 ANDA Products is canagliflozin. (*See* ZYDUS-INVOKA00000730 at 740; ZYDUS-INVOKA00023333 at 341; ZYDUS-INVOKA00067146-152; ZYDUS-INVOKA00024341-557; ZYDUS-INVOKA2_0430354-786.). [redacted]

40. Zydus' ANDA Products for the '542 ANDA contain a combination of two APIs. Zydus' '542 ANDA states that one of the APIs in the '542 ANDA Products is canagliflozin, and the other is metformin hydrochloride. (ZYDUS-INVOKA 00000730 at 738, 764.) Zydus' '542

ANDA Products include four dosage strengths, with the dosage of canagliflozin listed first and metformin hydrochloride listed second: a 50 mg/500 mg tablet, a 50 mg/1000 mg tablet, a 150 mg/500 mg tablet, and a 150 mg/1000 mg tablet. [redacted]

41. I have been provided with samples of Zydus' canagliflozin API and ANDA Products. (Ex. 6B.)

42. [redacted]

[redacted]

C. Methods to Characterize Solid Forms of Compounds

43. When a compound has been the subject of sufficient research and development regarding its solid-state structural properties, it may be possible to develop experimental protocols to identify whether a sample contains a given solid-state form. Those experimental protocols can consist of one or more analytical methods. In the sections below, I discuss two of those methods in more detail: XRPD and SSNMR, and more specifically fluorine-19 ("^{19}F") SSNMR.

1. X-Ray Powder Diffraction

44. XRPD is an analytical technique that can be used to identify the form of a crystalline compound, such as crystalline canagliflozin hemihydrate, and distinguish between different crystalline forms, which are colloquially referred to as "polymorphs." XRPD has been used to distinguish solid-state forms for decades, and is a standard technique in the field. (Ex. 7 at 2445-46.)

45. Where sufficient research and development has occurred on the solid-state properties of a compound using various analytical techniques, the unique XRPD pattern can be identified for different forms of the compound. Thus, it can be possible to develop an XRPD method that can be used to identify solid-state forms (polymorphs) of a compound in a given sample.

46. In XRPD (as used herein), X-rays are directed at a powder sample and the X-rays diffracted by the sample are detected by a diffractometer. A sample is placed within the XRPD instrument and the structures within the sample diffract incident radiation, or X-rays, based on

the orientation of the molecules. For crystalline materials, different crystalline structures typically diffract X-rays at different "scattering angles" (the angle of the incident X-ray beam to the crystal where scattering of the X-rays is observed) and at different "intensities" (how many X-rays are scattered). The scattering angles are measured and reported as diffraction peaks as a function of two theta ("2θ") ± 0.2 degrees 2θ. The 2θ values can be plotted against the differing intensities as "lines" or "peaks" to produce a diffraction pattern.

2. Solid-State NMR Spectroscopy (SSNMR)

a. General Background

47. SSNMR is an analytical technique that can be used to identify the form of a crystalline compound, such as crystalline canagliflozin hemihydrate, and distinguish between different polymorphs. SSNMR has been used to distinguish crystalline forms of a compound in the pharmaceutical field since at least the 1980's and is a standard technique in the field. (Ex. 8 at 2591-2605.)

48. SSNMR can be used in conjunction with other analytical techniques to determine what solid-state forms of a compound are contained within a given sample. For example, the SSNMR spectrum of solid-state forms can be obtained to determine the SSNMR characteristic peaks for different forms of a compound. Thus, it can be possible to develop an SSNMR method that can be used to identify solid-state forms (polymorphs) of a compound in a given sample.

49. In SSNMR, several techniques are used to obtain a high-resolution SSNMR spectrum of a sample. These techniques include magic-angle spinning, cross polarization, and high-power decoupling, described in more detail below.

50. SSNMR involves placing a sample into a very strong and homogeneous magnetic field. After being placed in the magnetic field, certain nuclei can be thought of as acting as small

magnets that are precessing[2] about an axis within the magnetic field. The NMR active nuclei in the sample align themselves approximately equally with and against the magnetic field, with a slight excess being aligned with the magnetic field. As the sample is pulsed with radio waves, some of the precessing nuclei will absorb this energy and flip their spin to oppose the magnetic field. These flipped nuclei are now precessing in a higher energy state. After the pulse, the nuclei begin to flip back to their original spin state, a process called relaxation that can take up to several seconds or even minutes for particular nuclei (*i.e.*, T_1 relaxation time). The precessing rate of the nuclei is detected and recorded by the SSNMR spectrometer. These precessing rates are then transformed into spectra, which contain information about the composition of the sample and chemical structure.

51. The NMR activity of a nucleus in the magnetic field is partially determined by the atom's atomic number (*i.e.*, number of protons in the nucleus of the atom) and mass number (*i.e.*, number of protons and neutrons in the nucleus of the atom). If both numbers are even, then the nucleus is not observable by SSNMR. If either is odd, then it is possible to observe the nucleus with SSNMR. This concept is important because an element, which always has the same number of protons in the nucleus, can have multiple isotopes, each with a different number of neutrons in the nucleus. Only certain isotopes produce an NMR signal, and therefore are useful for SSNMR, and it is often preferred to study non-quadrupolar nuclei. Compositions that contain one or more of the following nuclei are commonly analyzed using SSNMR spectroscopy: ^{13}C ("carbon-13"), ^{1}H ("proton"), ^{15}N ("nitrogen-15"), and ^{19}F ("fluorine-19"). All of these nuclei are non-quadrupolar. The sample being analyzed dictates the choice of nuclei to monitor by

[2] "Precession" is the rotation of the axis of a spinning body. A common example is the wobbling of a spinning top.

SSNMR. The natural abundance of the isotope also needs to be considered when deciding which isotope to monitor by SSNMR.

52. The following figure, from an article I co-authored, shows an example of SSNMR spectra of a non-quadrupolar nucleus (in this case ^{13}C) where magic-angle spinning, cross polarization, and high-power proton decoupling were applied and resulted in a high-resolution SSNMR spectrum of a pharmaceutically-related compound:

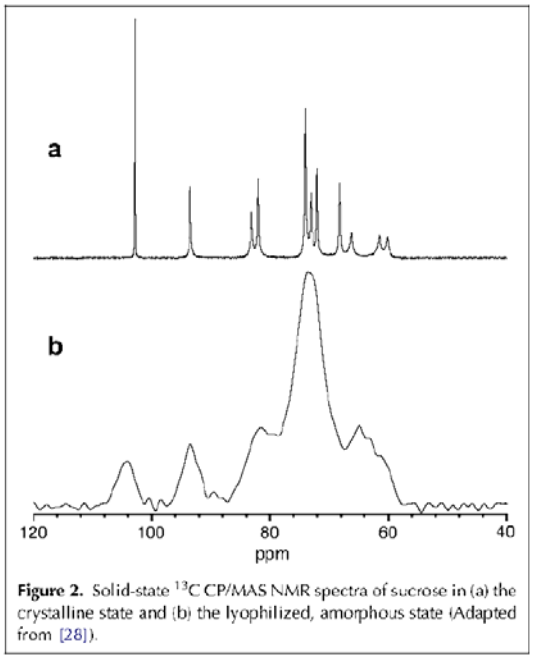


Figure 2. Solid-state ^{13}C CP/MAS NMR spectra of sucrose in (a) the crystalline state and (b) the lyophilized, amorphous state (Adapted from [28]).

(Ex. 9 at 981.)

53. A SSNMR spectrum is composed of peaks, with an x-axis that corresponds to chemical shifts, which are in units of parts per million (ppm), and a y-axis corresponding to peak intensity. Peaks in a SSNMR spectrum are located at chemical shifts that are a function of the local electronic environment surrounding the nucleus of an atom. In SSNMR, the electronic environment is affected by the functional groups of the compound, and by how the molecules are packed together (i.e., crystalline forms or amorphous). (Ex. 8 at 2593.) Thus, the chemical

shifts of the peaks in a SSNMR spectrum can give information about both the functional groups in a compound and a compound's solid-state form. (*Id.*)

54. SSNMR can determine whether a solid sample contains crystalline material or material that is amorphous. Crystalline forms have peaks where the "line widths" of the peaks (i.e. the full width at half height of the peaks) are typically about an order of magnitude less than the corresponding amorphous form of the material. In other words, a material in crystalline form has sharper/narrower SSNMR peaks than the corresponding amorphous form. A typical amorphous line width in ^{13}C SSNMR is 3-5 ppm, whereas crystalline peaks have line widths that are typically at about 1 ppm or less. In the figure I referenced above, the spectra are for sucrose in the crystalline state (a) and sucrose in the amorphous state (b):

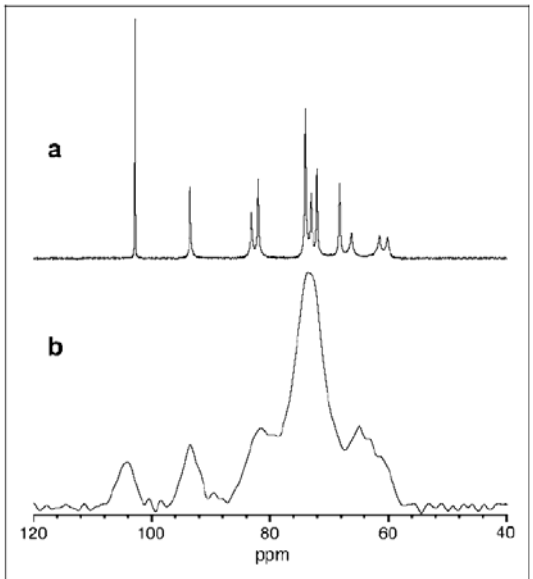


Figure 2. Solid-state ^{13}C CP/MAS NMR spectra of sucrose in (a) the crystalline state and (b) the lyophilized, amorphous state (Adapted from [28]).

(Ex. 9 at 981.) As can be seen in this example, the peaks for the crystalline material are sharper and narrower than the amorphous material. A similar type of change occurs for the other nuclei discussed previously, and in particular in ^{19}F SSNMR.

b. Flourine-19 SSNMR

55. ^{19}F SSNMR spectroscopy is a particularly powerful technique for investigating pharmaceutical compounds compared with studying other NMR active nuclei. When ^{19}F is present in a pharmaceutical compound, ^{19}F SSNMR can provide detailed information about crystalline forms as compared to amorphous forms, as well as different crystalline forms that may be present in a formulation. One advantage of ^{19}F SSNMR is that pharmaceutical excipients do not typically contain ^{19}F, and thus do not generate peaks in a ^{19}F SSNMR spectrum. In other words, if a peak is observed in a ^{19}F SSNMR spectrum, one knows that the peak was not created by one of the excipients. For Zydus' ANDA Products, I know that any peaks in the ^{19}F SSNMR spectrum are from canagliflozin because neither metformin hydrochloride nor any of the excipients used by Zydus in its ANDA Products contain fluorine.

56. Another advantage of ^{19}F SSNMR, compared with SSNMR of other commonly-observed nuclei, is that ^{19}F is an NMR-active nuclei that is approximately 100% naturally abundant. That means that essentially all fluorine atoms will generate an SSNMR signal. By contrast, carbon atoms contain only 1.1% of ^{13}C nuclei, with most of the rest of the carbon atoms containing the NMR inactive ^{12}C nuclei. Nitrogen atoms contain only 0.34% of ^{15}N nuclei, with most of the rest of the nitrogen atoms containing ^{14}N, which is a quadrupolar nucleus.

c. Techniques for Obtaining a High-Resolution ^{19}F SSNMR Spectrum

57. In order to acquire a high-resolution ^{19}F SSNMR spectrum in the solid state, there are several techniques that should be applied, and which were applied in my work on this project. (*See, e.g.,* Ex. 8; Ex. 9; Ex. 10.) The first is called magic-angle spinning ("MAS"). MAS is a technique that takes broad SSNMR signals and makes them sharper in a SSNMR spectrum. Solid samples have molecules, or groups of molecules, that are fixed in their orientation in the magnetic field. These fixed orientations result in a distribution of chemical shifts for the sample,

known as chemical shift anisotropy, which broadens the peaks in the spectrum. MAS is performed by spinning the sample at an angle of 54.7 degrees with respect to the static magnetic field. When this occurs, the distribution of chemical environments is averaged so that only the isotropic, or average, chemical-shift value is observed. This makes the peaks narrower, thereby improving resolution and making it easier to distinguish different peaks from each other. However, one potential result of MAS is the generation of artifacts in the SSNMR spectra called "spinning sidebands." Spinning sidebands appear at known locations in the SSNMR spectrum that are defined by how fast the sample was spun. If necessary, spinning sidebands can be separated from the isotropic chemical shifts by varying the spinning speed of the sample. When the spinning speed of the sample is changed, the chemical shifts of the isotropic speed will not change, but the spinning sidebands will change at known values based upon the spinning speed.

58. A second technique that is used to improve the resolution of a ^{19}F SSNMR spectrum is to decouple the protons (i.e. ^{1}H nuclei) from the ^{19}F nuclei. In the solid state, the fixed orientations of the protons that are coupled to ^{19}F may result in a broadening of the peaks in the ^{19}F SSNMR spectrum. By applying a strong radiofrequency signal at the resonance frequency of the protons, the protons can be "decoupled" from ^{19}F, resulting in a narrower peak in the ^{19}F SSNMR spectrum.

59. Another technique that can improve the efficiency of ^{19}F SSNMR is called "cross polarization." In ^{19}F SSNMR, the spin-lattice relaxation times (T_1) of the ^{19}F SSNMR nuclei may be very long. Longer relaxation times mean that a fewer number of individual data acquisitions can be added together in a given amount of time. Fewer acquisitions mean a worse signal to noise ratio, leading to relatively poorer sensitivity compared to the sensitivity that would otherwise be obtained with more acquisitions. Cross polarization is a method that uses the

relaxation time of a different nucleus, such as a hydrogen nucleus (a proton or ^{1}H), which has a shorter relaxation time, to increase the number of acquisitions per unit time, resulting in increased sensitivity. In addition, cross polarization can be used to improve the signal to noise ratio of the spectrum for certain nuclei. Cross polarization typically works by transferring magnetization from abundant nuclei, such as ^{1}H, to less abundant nuclei, such as ^{13}C, that often have a long T_1 relaxation time as well as a low magnetogyric ratio, which for ^{13}C is one-quarter of the value compared to ^{1}H. The proton or ^{1}H nuclei transfer their magnetization to nearby ^{13}C nuclei, which then relax and the signal is collected. In ^{19}F SSNMR, cross-polarization can sometimes be beneficial because the proton relaxation time is often much shorter than the fluorine relaxation time.

60. When SSNMR is conducted properly, the technique gives consistent results for a well-characterized compound. Different samples of a compound typically will generate the same peaks at about the same location in a ^{19}F SSNMR spectrum ± 0.4 ppm.[3]

d. Techniques for Selectively Observing Forms in a SSNMR Spectrum

61. When there are two or more components in a sample, it is possible with SSNMR to selectively reduce the signal from certain components based upon the SSNMR properties of those components. Components in this case can refer to different compounds, or even the same compound but in different forms, e.g. crystalline and amorphous, or two different crystalline forms. This approach is especially useful when the component of interest is present at lower levels in the sample. For example, when a sample contains a crystalline form mixed with a

[3] ^{19}F SSNMR has a margin of error of typically ±0.4 ppm, depending upon linewidth. Because the location of peaks can be affected by the reference point, which can shift slightly, the location of the peaks for a particular compound can vary slightly when tested on different machines or if the spectra were referenced slightly differently. Differences in referencing will result in a consistent shift of all of the peak locations in the spectrum.

larger amount of the amorphous form of the same compound, the strong signal from the amorphous material can make it difficult to detect the signal from the crystalline material.

62. One method to selectively observe a component present at relatively lower levels in a sample with a mixture of components is to use an approach described here as the "$T_{1\rho}$ spin lock." This method utilizes differences in the spin-lattice relaxation time in the rotating frame (referred to as $T_{1\rho}$) between different components of the mixture. For example, amorphous and crystalline materials can have very different proton $T_{1\rho}$ values. (Ex. 8 at 2591-2605; Ex. 10 at 1008-1017.) In particular, the nuclei of crystalline materials can have significantly longer $T_{1\rho}$ relaxation times than the nuclei of amorphous materials, and in particular, longer proton $T_{1\rho}$ relaxation times. That is because the higher molecular mobility in the amorphous form provides a mechanism for relaxation. (Ex. 8 at 2593.)

63. When a particular crystalline component has a significantly longer proton $T_{1\rho}$ relaxation time compared to the amorphous component, we can select the settings of the ^{19}F SSNMR experiment to detect the signal from the crystalline material that is mixed with the amorphous material. When we increase the proton spin-locking time, the signals generated by nuclei that have a short proton $T_{1\rho}$ relaxation time will decay more quickly, while the signals generated by nuclei that have a long proton $T_{1\rho}$ relaxation time will decay more slowly. As a result of this phenomenon, at longer proton spin-locking times, signals from amorphous materials with a short relaxation time will have decayed more significantly than signals from crystalline materials with a long relaxation time. Thus, one can more readily detect signals from crystalline materials in a mixture of amorphous and crystalline materials by setting higher proton spin locking times.

64. Consider an example where the amorphous material's relaxation time ($T_{1\rho}$) is 10 ms and the crystalline relaxation time ($T_{1\rho}$) is 80 ms. If we set the proton spin-locking time at 50 ms, 99.3% of the amorphous signal would no longer be present due to natural decay. By contrast, only 54% of the crystalline signal would no longer be present due to natural decay. As a result, the low signal from the amorphous material at the 50 ms collection time does not obscure the signal from the crystalline material. This method can therefore be used to focus on detection of the signal from the crystalline material.

65. My colleagues and I have published several papers containing examples that show how differences between the proton $T_{1\rho}$ values of crystalline and amorphous forms of compounds can be used to detect and identify the crystalline component in a sample that contains primarily amorphous material. (Ex. 10, Sotthivirat, et al., *J. Pharm. Sci*. 96 (2007).)

66. In the Sotthivirat article, I used this approach to detect the presence of crystalline prednisolone (PDL) in a mixture with amorphous cyclodextrin (CD). (Ex. 10.) I have reproduced Figure 3 of the Sottivirat paper for reference below. Figure 3 shows graphically how the signal intensity decreases significantly for the material with the short $T_{1\rho}$ relaxation time, cyclodextrin or CD, whereas the signal intensity of the material with the long $T_{1\rho}$ relaxation time, prednisolone or PDL, does not decrease significantly. This example illustrates that this technique can be used to detect the signal from the crystalline material in the presence of a larger amount of amorphous material in the sample. Even though the example is shown for ^{13}C SSNMR, the method is equally applicable to both ^{13}C and ^{19}F SSNMR.

67. Below, I have reproduced Figures 3b-3d from the Sottivirat paper, which show how the technique works. Figure 3b is the spectrum of the crystalline prednisolone acquired using a 2 ms contact time and Figure 3c is the mixture of the amorphous cyclodextrin and

crystalline prednisolone acquired using a 2 ms contact time. In Figure 3c, even though the prednisolone is less than 10% of the formulation by weight, the peaks are very evident in the spectrum. In Figure 3d, $T_{1\rho}$ spin lock is applied to the same sample used in Figure 3c and the crystalline prednisolone peaks are even more evident in the spectrum.

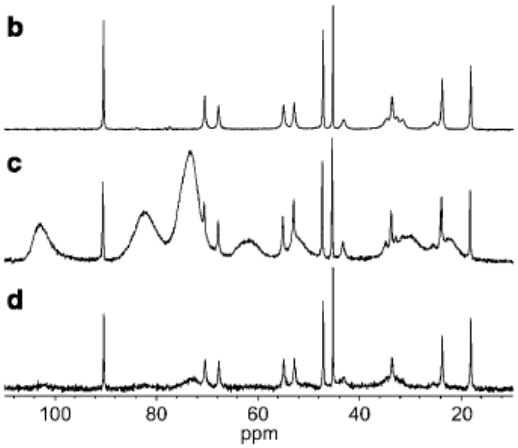


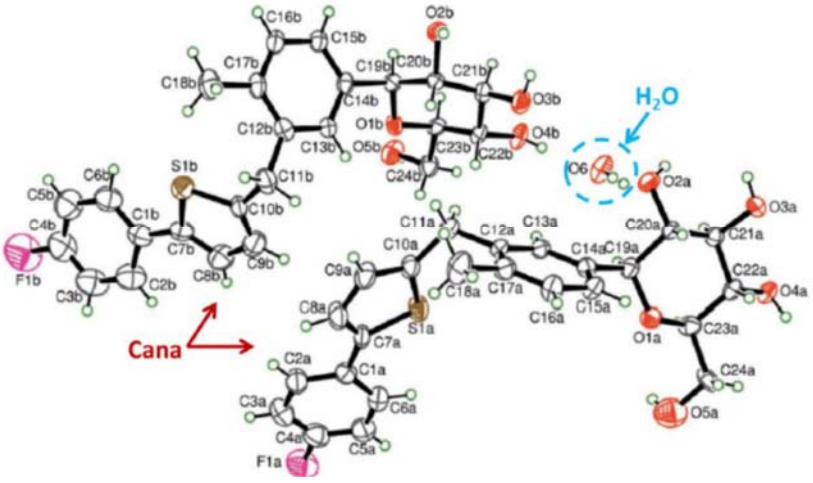
Figure 3. (a) Plot of normalized CD and PDL peak areas as a function of contact time, and ^{13}C solid-state NMR spectra from 10–110 ppm of (b) crystalline PDL form II acquired with a 2-ms contact time; (c) a physical mixture of CD and PDL form II in a 2:1 CD to PDL molar ratio, acquired using a 2-ms contact time; and (d) a physical mixture of CD and PDL form II in a 2:1 CD to PDL molar ratio, acquired using a 7-ms contact time.

(Ex. 10 at 1011.)

D. Characterization of Solid Forms of Canagliflozin

68. Canagliflozin is a compound that has been extensively studied for over ten years and has been well characterized by multiple testing techniques, including XRPD, NMR, SSNMR, Raman spectroscopy, IR spectroscopy, DSC, and TGA. In addition, the full 3-D crystal structure of crystalline canagliflozin hemihydrate has been determined. (*See* Ex. 11, Kai-Hang Liu, Acta. Cryst. 72 (2016) at 734-736.) [redacted]

69. Of particular significance for my analysis, ^{19}F SSNMR can be used to identify different forms of canagliflozin. To help understand why, I have included a figure below showing the structure of crystalline canagliflozin hemihydrate, where there are two molecules of canagliflozin (each having one fluorine atom) and one water molecule:



(Ex. 11 at 734-736.) The fluorine atoms are shown in purple (F1a and F1b), and the water is circled in blue.

70. As noted above, the canagliflozin hemihydrate crystal structure has two molecules of canagliflozin and one molecule of water. Canagliflozin hemihydrate has approximately half a molecule of water for every molecule of canagliflozin.

71. [redacted]

[redacted]

[redacted]

[redacted]

72. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4 [redacted]

73. [redacted]

74. [redacted]

75. [redacted]

[redacted]

77. [redacted]

VIII. MATERIALS AND METHODS

78. Below are the details for the samples analyzed, the chain of custody, and the analytical methods applied.

A. Samples Analyzed And Chain of Custody

79. Table 1 below sets forth information regarding the canagliflozin hemihydrate material that I tested. I understand that the "Janssen Batch No." is a designation assigned by Janssen. The "LIMS No." is a numeric identifier assigned by AMRI SSCI, LLC ("SSCI"). The "KAS Sample No." is an identifier assigned to the sample by Kansas Analytical Services.

Table 1

Janssen Batch No.	LIMS No.	KAS Sample No.	Quantity	Description
18LG44413	509705	KAS0917044	1054.64 mg	Canagliflozin API

80. I understand that Plaintiffs provided the canagliflozin hemihydrate to Karen Gushurst of SSCI in West Lafayette, Indiana. The material in Table 1 was stored at SSCI according to the storage instructions provided, [redacted] (Ex. 6A.)

81. Table 2 below sets forth information regarding the samples of Zydus' API and ANDA Products. I understand that the "Zydus Batch No." is a designation assigned by Zydus.

Table 2

Zydus Batch No.	LIMS No.	KAS Sample No.	Quantity	Description
CUa0190616	485673	KAS0917019	209.55 mg	Canagliflozin API
0908430346	523823	KAS0917063	507.60 mg	Canagliflozin API
ME68475	485683	KAS0917020	2 tablets	Canagliflozin Tablets 300 mg Film Coated Tablets

ME68463	468939	KAS0917038	2 tablets	Canagliflozin Tablets 100 mg Film Coated Tablets
	500998	KAS0917039	2 tablets	Canagliflozin Tablets 100mg Film Coated Tablets
	500999	KAS0917041	2 tablets	Canagliflozin Tablets 100mg Film Coated Tablets
	501000	KAS0917042	2 tablets	Canagliflozin Tablets 100mg Film Coated Tablets
ME68463	468940	KAS0917043	2 tablets	Canagliflozin Tablets 100 mg Film Coated Tablets
	500995	KAS0917045	2 tablets	Canagliflozin Tablets 100mg Film Coated Tablets
	500996	KAS0917046	2 tablets	Canagliflozin Tablets 100mg Film Coated Tablets
	500997	KAS0917047	2 tablets	Canagliflozin Tablets 100mg Film Coated Tablets
ME68512	485698	KAS0917054	2 tablets	Canagliflozin/Metformin Hydrochloride Tablets 150 mg Canagliflozin / 500 mg Metformin Hydrochloride Film Coated Tablets
ME68514	485699	KAS0917055	2 tablets	Canagliflozin/Metformin Hydrochloride Tablets 150 mg Canagliflozin / 500 mg Metformin Hydrochloride Film Coated Tablets
ME68516	485700	KAS0917056	2 tablets	Canagliflozin/Metformin Hydrochloride Tablets 150 mg Canagliflozin / 1000 mg Metformin Hydrochloride Film Coated Tablets
ME68520	485702	KAS0917057	2 tablets	Canagliflozin/Metformin Hydrochloride Tablets 150 mg Canagliflozin / 1000 mg Metformin Hydrochloride Film Coated Tablets
ME68523	485703	KAS0917058	2 tablets	Canagliflozin/Metformin Hydrochloride Tablets

				150 mg Canagliflozin / 1000 mg Metformin Hydrochloride Film Coated Tablets
ME68500	485692	KAS0917048	2 tablets	Canagliflozin/Metformin Hydrochloride Tablets 50 mg Canagliflozin / 500 mg Metformin Hydrochloride Film Coated Tablets
ME68502	485693	KAS0917049	2 tablets	Canagliflozin/Metformin Hydrochloride Tablets 50 mg Canagliflozin / 500 mg Metformin Hydrochloride Film Coated Tablets
ME68504	485694	KAS0917050	2 tablets	Canagliflozin/Metformin Hydrochloride Tablets 50 mg Canagliflozin / 500 mg Metformin Hydrochloride Film Coated Tablets
ME68506	485695	KAS0917051	2 tablets	Canagliflozin/Metformin Hydrochloride Tablets 50 mg Canagliflozin / 1000 mg Metformin Hydrochloride Film Coated Tablets
ME68508	485696	KAS0917052	2 tablets	Canagliflozin/Metformin Hydrochloride Tablets 50 mg Canagliflozin / 1000 mg Metformin Hydrochloride Film Coated Tablets
ME68510	485697	KAS0917053	2 tablets	Canagliflozin/Metformin Hydrochloride Tablets 50 mg Canagliflozin / 1000 mg Metformin Hydrochloride Film Coated Tablets

82. These samples were sent by Zydus to Karen Gushurst at SSCI. (Ex. 6B.)

83. The samples in Table 2 were stored at SSCI at controlled room temperature, because they were shipped by Zydus to SSCI at ambient conditions. (Ex. 6B at ¶10]). I reviewed a declaration of Karen Gushurst, which confirms that SSCI stored the samples in closed

containers at controlled room temperature. (*Id.*) SSCI stored the samples in a room where the environment is kept at standard laboratory conditions. (*Id.*)

84. Karen Gushurst transferred a portion of each of the materials referenced in Tables 1 and 2 above to Kansas Analytical Services.[5] The samples of Zydus' API and ANDA Products were received packaged in tightly closed amber glass bottles with screw top lids wrapped in parafilm. (*Id.*) The amber glass bottles were packaged inside a first Ziploc bag with the desiccant Drierite, which was contained in a second Ziploc bag, which was wrapped in bubble wrap. That was packaged in a Uline insulated container within a FedEx box. (*Id.*)

85. The samples of the canagliflozin hemihydrate that were shipped to Kansas Analytical Services were [redacted] Ex. 6A.)

86. All of the samples that referenced in Tables 1 and 2 were stored at Kansas Analytical Services [redacted] in which they were packaged when they were received, in a secure locker [redacted] in a climate-controlled building.

B. Experimental Methods

87. At my direction and under my supervision, Matthew Nethercott, Ph.D., an employee at Kansas Analytical Services, ran the samples on the SSNMR spectrometer. He routinely runs SSNMR spectra at my direction. I reviewed all of his work and performed all of the data processing and spectral analysis in this report using the raw data files.

[5] I have a partial ownership interest in and am a Senior Consultant at Kansas Analytical Services, and routinely direct work conducted there.

88. The SSNMR experiments were performed on a Bruker 400 MHz NMR spectrometer. Niflumic acid was used as a tune-up standard to ensure that the spectrometer was operating properly. All spectra were referenced to the peak for the fluorinated methyl group in the niflumic acid reference standard, which had a chemical shift of -60.5 ppm. All data were processed using 20 Hz of exponential apodization, a dataset size of 16k, and an effective free induction decay length of 2000 points. All spectra were phased manually.

89. The instrument is calibrated before and after each sample, and is serviced if it fails to meet the calibration standards set by the Kansas Analytical Services. (Ex. 13.)

90. All raw data files from the SSNMR experiments are provided in Exhibit 22. Spectra generated from the SSNMR experiments are provided in Exhibit 31.

91. For all samples, approximately 50 mg of sample was packed into a 4 mm ceramic rotor. Powder samples were prepared by taking a powder and loading it directly into the NMR rotor prior to analysis. Tablet samples were gently broken up into smaller pieces prior to placing them into the NMR rotor. A sample packing tool was used to gently compact all samples prior to insertion of the rotor cap. Samples were spun at a rate of 10 kHz with active spin speed control. Log pages relating to these experiments are provided in Exhibits 23-30.

92. Four kinds of experiments were performed. The first experiment was a cross polarization experiment to obtain the spectrum of the sample. The second and third experiments were used to determine relaxation values. To measure the proton spin-lattice relaxation ($^1H\ T_1$), a saturation recover experiment with cross polarization was used. To measure the proton spin lattice relaxation time in the rotating frame ($^1H\ T_{1\rho}$), a cross polarization experiment with a proton spin lock prior to cross polarization was used. The fourth type of experiment, $T_{1\rho}$ spin

lock, was a variation of the experiment used to measure the proton spin-lattice relaxation time in the rotating frame, where the spin lock field was applied for 128 ms.

93. Individual experimental parameters, such as relaxation delays, contact times, number of acquisitions, etc., can be found in the attached raw data files.

94. I directed XRPD testing at SSCI. Per SSCI, the XRPD patterns were collected with a PANalytical X'Pert PRO MPD diffractometer using an incident beam of Cu radiation produced using an Optix long, fine-focus source. (Ex. 18; Ex. 19; Ex. 14 at 7-8.) An elliptically graded multilayer mirror was used to focus Cu Kα X-rays through the specimen and onto the detector. A silicon specimen (NIST SRM 640e) was analyzed to verify the observed position of the Si 111 peak is consistent with the NIST-certified position. A specimen of the sample was sandwiched between 3-µm-thick films and analyzed in transmission geometry. A beam-stop, short antiscatter extension, and an antiscatter knife edge were used to minimize the background generated by air. Soller slits for the incident and diffracted beams were used to minimize broadening from axial divergence. Diffraction patterns were collected using a scanning position-sensitive detector (X'Celerator) located 240 mm from the specimen and Data Collector software v. 5.5. XRPD peak picking was performed using SSCI's in-house software, PatternMatch 3.0.4.

95. The diffractometers at SSCI undergo a daily intensity verification and verification of 2θ angle measurement every day of use. Compliance for the angle measurement is 28.441° ±0.020° for the Si Kα1 component of the Si 111 peak.

96. All of the raw data files from the XRPD experiments are provided in Exhibit 21. XRPD patterns generated by the XRPD by the XRPD experiments are provided in Exhibits 15-17.

IX. ANALYSIS & DISCUSSION

A. [redacted]

97. I was asked to opine on whether [redacted]. In my opinion, [redacted].

1. [redacted]

98. [redacted]

[redacted]

99. [redacted]

100. [redacted]

[redacted]

[redacted]

[redacted]

101. [redacted]

[redacted]

[redacted]

102. [redacted]

[redacted]

6 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

104. [redacted]

[redacted]

[redacted]

[redacted]

HIGHLY CONFIDENTIAL

[redacted]

[redacted]

[redacted]

[redacted].

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7 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

112. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8 [redacted]

[redacted]

115. [redacted]

[redacted]

116. [redacted]

[redacted]

120. [redacted]

124. [redacted]

[redacted]

125. [redacted]

[redacted]

[redacted]

[redacted]

128. [redacted]

129. [redacted]

130. [redacted]

[redacted]

[redacted]

135. [redacted]

[redacted]

[redacted]

136. [redacted]

137. [redacted]

[redacted]

[redacted]

[redacted]

142. [redacted]

[redacted]

143. [redacted]

[redacted]

[redacted]

144. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

148. [redacted]

[redacted]

[redacted]

[redacted]

152. [redacted]

[redacted] For each sample, [redacted]

[redacted]

[redacted]

156. [redacted]

[redacted]

[redacted] For each sample, [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] In my opinion, [redacted]

[redacted]

C. Zydus' API And Proposed ANDA Products Infringe Claim 1

161. It is my opinion that Zydus' ANDA Products infringe claim 1 of the '582 patent. Claim 1 recites: "A crystalline form of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate." Claim 1 includes two limitations: (1) canagliflozin and (2) that the canagliflozin is in a hemihydrate crystalline form. I understand that in order to infringe claim 1, Zydus' ANDA Products must meet both of those limitations.

162. Zydus' documents confirm that its API and proposed ANDA Products contain canagliflozin.

[redacted]

[redacted]. As a result, it is my opinion that Zydus' ANDA Products infringe claim 1 of the '582 patent.

D. Zydus' API And Proposed ANDA Products Infringe Claim 3

164. It is my opinion that Zydus' ANDA Products infringe claim 3 of the '582 patent. Claim 3 recites: "A crystalline form of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate of claim 1, having substantially the same X-ray diffraction pattern as set out in FIG. 1." Claim 3 includes the two limitations of claim 1, including (1) canagliflozin and (2) that the canagliflozin is in a hemihydrate crystalline form. Claim 3 also requires (3) that the crystalline form have substantially the same X-ray diffraction pattern as set out in FIG. 1 of the '582 patent. I understand that in order to infringe claim 3, Zydus' ANDA Products must meet all three of those limitations.

165. Zydus' documents confirm that its proposed ANDA Products contain canagliflozin.

166. As I explained above in paragraphs, it is my opinion that samples of Zydus' API and proposed ANDA Products analyzed for this report contain the crystalline canagliflozin hemihydrate form of Figure 1 of the '582 patent. [redacted]

167. Thus, the crystalline canagliflozin hemihydrate present in Zydus' API and ANDA Products is the same form of Figure 1 of the '582 patent. It will therefore have an XRPD pattern that is substantially the same as the XRPD pattern of Figure 1.

168. For these reasons, it is my opinion that the proposed ANDA Products that Zydus will manufacture and sell pursuant to its '541 ANDA and '542 ANDA will include tablets that contain the canagliflozin hemihydrate form of Figure 1 of the '582 patent.

169. Accordingly, Zydus' ANDA Products meet all of the limitations of Claim 3 of the '582 patent. Thus, it is my opinion that Zydus' API and proposed ANDA Products infringe Claim 3 of the '582 patent.

X. SUPPLEMENTATION

170. I reserve the right to supplement or amend my report in response to opinions expressed by Zydus' experts, or in light of additional evidence, testimony, discovery, or other information that may be provided to me after the date of this report.

171. I also reserve the right to offer additional testimony, if necessary, concerning the subject matter of the patents-in-suit.

172. In addition, I expect that I may be asked to consider and testify about issues that may be raised by Zydus' fact witnesses and technical experts at trial or in their reports. It may also be necessary for me to supplement my report as a result of ongoing discovery, Court rulings and testimony at trial.

XI. TRIAL EXHIBITS

173. I may rely on visual aids and demonstrative exhibits that demonstrate the bases for my opinions. These visual aids and demonstrative exhibits may include, for example, interrogatory responses, deposition testimony and exhibits, as well as charts, photographs, diagrams, videos, and animated or computer-generated videos.

Executed this 7th day of February 2020. I declare under penalty of perjury that the foregoing is true and correct.

Eric J. Munson, Ph.D.